

McCullom (John H.)



# ANTITOXINE IN THE TREATMENT OF DIPHTHERIA.

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BY JOHN H. MCCOLLOM, M.D.  
OF BOSTON.

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## ANTITOXINE IN THE TREATMENT OF DIPHThERIA.

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It is the generally conceived opinion that physicians are exceptionally conservative in accepting any new remedy for the treatment of any special disease, and it is well that it should be so; for only by careful investigation of the results of any special mode of treatment can we hope to arrive at the truth. Statistics of the result of any method of treatment of a special disease, to be of value, must be based on a large number of cases and must continue for a very considerable period of time. It is also important that the cases should be observed until absolute recovery takes place. Antitoxine has now been in use something over three years, and the consensus of opinion is that it is a remedy of great value in the treatment of diphtheria. It has not, however, proved of advantage in far advanced septic cases of this disease, neither has it been shown to be of any value in the later symptoms characterized by failure of the heart's action and a general degeneration of the nerves. While it is not claimed that antitoxine will cure every case of diphtheria, it is claimed, and an analysis of the following statistics proves, that the serum of horses rendered immune to the toxine of diphtheria is one of the most valuable agents in the treatment of diphtheria. In the Boston City Hospital in 1891 there were 237 cases of diphtheria treated, with 105 deaths. In 1892-3 there were 387 cases treated, with 185 deaths. In 1893-4 there were 438 cases treated, with 203 deaths. In 1894-5, when anti-

toxine was used only in a comparatively small proportion of cases, there were 698 cases treated, with 266 deaths, making a total of 1760 cases with 759 deaths, with a percentage of 43, which was about the average death-rate of diphtheria in hospital cases both in this country and in Europe. In private practice the death-rate as a rule is not quite so high as in hospital cases, simply from the fact that the severe cases only are sent to the hospital. In Boston, from 1878 to 1894, the average death-rate in the city was 30.7. The lowest death-rate was 27.18 and the highest 35.7. As this comprises 24,813 cases, the average fatality of the disease can be readily seen. In the South Department of the Boston City Hospital, from the first of September, 1895, to the first of May, 1896, when every case was treated with antitoxine, there were 1359 cases of diphtheria treated, with 170 deaths, giving a percentage of 12.50. In the year 1895 throughout the whole city there were 4059 cases reported to the Board of Health, with 588 deaths and a percentage of 14.48. These cases reported to the Board of Health include many mild cases and therefore cannot give a proper idea of the death-rate of this disease. Some of these cases were without doubt treated with antitoxine, but how many it is impossible to state. The cases in the South Department of the Boston City Hospital, on the other hand, were nearly all of them severe cases and in many instances the membrane covered the tonsils, the uvula and nearly the whole of the roof of the mouth, with extensive swelling of the cervical glands. As a rule patients are not sent to a hospital unless they are seriously ill, and for this reason statistics based on hospital cases give a much better idea of the benefit of any prescribed method of treatment than can be obtained from cases in private practice. It is claimed, and with truth, that in the first year of life diphtheria is an extremely fatal disease, the majority of patients succumbing to it.



An analysis of the cases at the hospital shows that in eight months there were 17 cases admitted under one year of age with three deaths, giving a percentage of 17.6. The number of patients from one to two years old admitted was 74 with 20 deaths, giving a percentage of 27; from two to three years of age there were 136 patients admitted with 37 deaths, giving a percentage of 27; from three to five years of age 329 patients were admitted with 55 deaths, a percentage of 16.7; from five to ten years there were 410 patients admitted with 39 deaths, giving a percentage of 9.5; from ten to twenty years 187 patients with 9 deaths, giving a percentage of 4.8; and from twenty years and upwards 206 patients with 7 deaths, a percentage of 3.4. All of these cases were treated with antitoxine, and it would seem that these statistics should convince any one of the beneficial effects of this agent. If we take the highest death-rates occurring in any of these ages, namely that from one to two years, and also from two to three years, children of these ages being particularly susceptible to the disease, and in whom diphtheria plays the greatest havoc, we find that the death-rate is 27 as compared with 43 before antitoxine was used—a marked diminution.

In the epochs of life from five to ten years, from ten to twenty years, and from twenty years upwards, there is an extremely low death-rate, being respectively 9.5, 4.8 and 3.4. There would seem to be only one explanation of this low death-rate. In all of these cases antitoxine was administered within a very short time after the admission of the patients. Bacteriological examinations were made in every instance, but it was not deemed advisable to wait for the result of the cultures before administering the serum. In order to obtain the best results from the use of the anti-diphtheritic serum, it is important to administer the agent early in the disease. A delay of 24 hours after the appearance of the membrane frequently imperils the lives of the patients. In

a case of well-marked clinical diphtheria the time necessary for the growth of the organism in the culture tube is lost, but it is very important that cultures should be made in each and every case of diphtheria in order that statistics may be based on a scientific foundation. The failure to obtain a positive result has occurred so seldom as not to be a factor of the slightest value, as this failure has been due to some error in technique. The importance of the early administration of antitoxine is shown by an examination of the statistics of the hospital. Of the 1,359 cases admitted 53 died within 24 hours of admission, and of these 53 quite a large number died within two or three hours. If we eliminate these 53 cases we have 1,306 cases and 117 deaths, a percentage of 8.9. If we eliminate the 74 deaths that occurred within 48 hours of admission, we have a percentage of 7.4.

Table of the number of cases of diphtheria, treated at the Boston City Hospital, with the deaths, by ages, from Sept. 1, 1895, to May 1, 1896:—

AGES.	CASES.	DEATHS.
1 year . . . . .	17 . . . . .	3
1-2 years . . . . .	74 . . . . .	20
2-3 “ . . . . .	136 . . . . .	37
3-5 “ . . . . .	329 . . . . .	55
5-10 “ . . . . .	410 . . . . .	39
10-20 “ . . . . .	187 . . . . .	9
20 years and upwards . . . . .	206 . . . . .	7

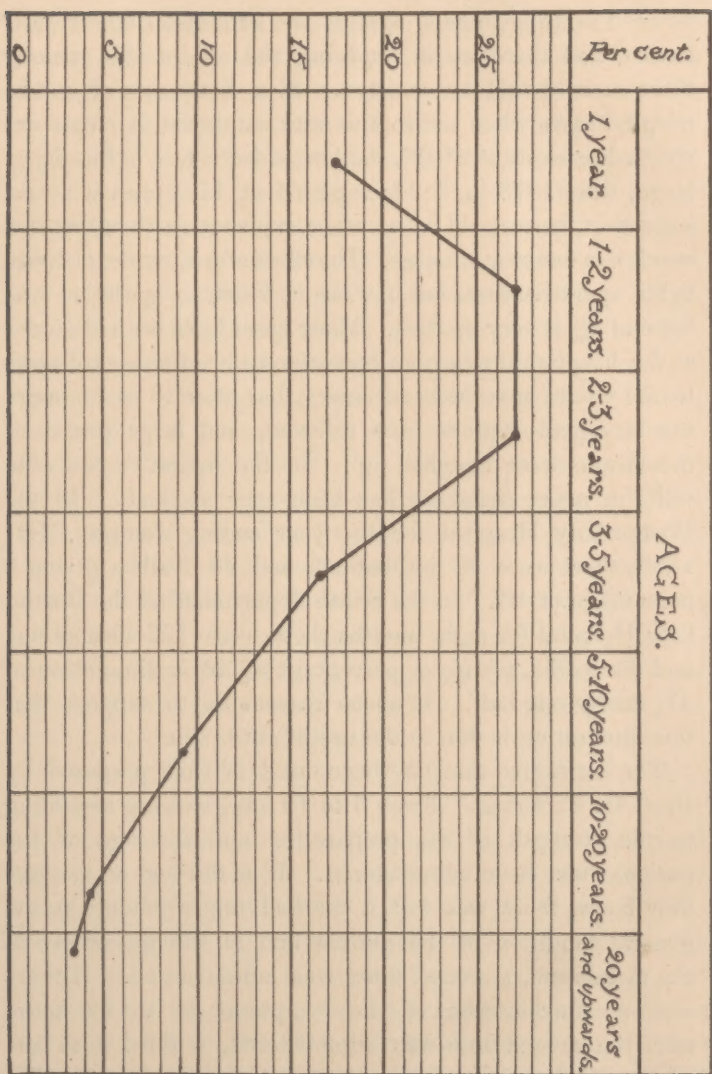
Cases in which antitoxine was used:—

1359 with 170 deaths, per cent. 12.50.

Cases from February, 1891, to February, 1894, in which antitoxine was not used:—

1062 with 493 deaths, per cent. 46.

CHART OF THE PERCENTAGE OF DEATHS FROM DIPHTHERIA, BY AGES, AT THE SOUTH DEPARTMENT OF THE BOSTON CITY HOSPITAL, FROM SEPT. 1, 1895, TO MAY 1, 1896.





It is manifestly evident that moribund cases should not be used as an argument against the administration of antitoxine, and therefore in studying the use of this remedy these cases should be omitted. If a death-rate of 8.9 in hospital cases when antitoxine was employed is compared with a death-rate of 27.06, the lowest death-rate in the city at large, from 1878 to 1894, a period of 17 years, it would seem that there could be no other explanation than that this result was due to antitoxine. The effect of antitoxine, not only in the operative cases but in those in which an operation was impending, is very marked. Many cases have been observed at the hospital in which an operation before the days of antitoxine would have been necessary, but after 18 to 24 hours the laryngeal stenosis was relieved, and large pieces of membrane were coughed up. In the operative cases the relief in many instances has been very marked. In the Boston City Hospital for the year ending January 31st, 1895, there were 89 intubations and 74 deaths, giving a percentage of 83. In the South department of the Boston City Hospital for eight months there were 136 intubations and 63 deaths, giving a percentage of 46, a diminution of 37, nearly one half. It seems reasonable to suppose that this diminution is due to the use of antitoxine.

The antitoxine that has been used is that prepared by Prof. H. C. Ernst. From 5 to 10 c.c., varying according to the strength of the preparation and the age of the patient, have been administered. If at the end of twenty-four hours there was not a marked improvement in the general condition of the patient and in the appearance of the membrane, a second dose was administered. If there was no amelioration of the symptoms 24 to 32 hours after the second dose was administered, a third dose was given, and in certain instances a fourth dose. The appearance of the membrane in favorable cases caused by the action of the antitoxine is very characteristic. The



membrane commences to be detached at the edges, is undermined and begins to roll up. This appearance is so characteristic that when it has occurred a second dose has not been given. In no instance has the membrane ever re-formed to any considerable extent. In septic cases the septic odor in the majority of instances has been less apparent after the administration of antitoxine. The stronger the antitoxine is, the better; because it is necessary to inject a less quantity, as can be readily understood. An injection of 20 c.c. into the cellular tissue causes quite a perceptible tumor, and is a source of annoyance to the patient, therefore a preparation in which the requisite dose is from 5 to 10 c.c. is better than one in which the dose is 20 c.c. The method of estimating the dose of antitoxine by normal units is perhaps the better one. An antitoxine unit is an amount of serum required to protect a guinea pig weighing 500 grammes from the minimum fatal dose of the toxine of diphtheria. The number of immunity units per c.c. would give the strength of the serum; for example, one one-hundredth of a c.c. would protect a guinea pig weighing 500 grammes, and for a person weighing 120 pounds, or about 50,000 grammes, 1 c.c. would be required for procuring immunity. For the cure of the disease, however, fifteen or twenty times as large a dose is required, namely, 1,500 to 2,000 units.

In no instance has any serious effect followed the use of antitoxine at the hospital. In a few instances abscesses have appeared at the point of injection. Cultures made from the contents of these abscesses showed a pure growth of streptococci, and as abscesses are not infrequently concomitants of diphtheria, it is reasonable to suppose that the injection of antitoxine was only an exciting cause of a predisposing condition of the system. As illustrating this point, two sisters with severe attacks of diphtheria were injected at the same time with the same specimen of anti-

toxine. One had a large cervical abscess from which a pure culture of streptococci was taken, the other had a small abscess at the point of inoculation which also gave a pure growth of streptococci. The injection of antitoxine had certainly nothing to do with the cervical abscess and it is at least doubtful if the injection was the direct and immediate cause of the second abscess. It is a significant fact that pure cultures of streptococci have been obtained from all the cervical abscesses at the hospital occurring in the course of diphtheria.

Severe joint pains have been noticed in five instances. These attacks have generally lasted from twenty-four to forty-eight hours, and have been a source of annoyance to the patients, but in no instance have they been an element of danger.

Urticaria has occurred in quite a number of cases, and although this has been a cause of discomfort to the patient, it has never been a grave symptom. Dermatitis resembling the eruption of a severe attack of scarlet fever in which the diagnosis for the first twenty-four hours was impossible, has been noticed in a few instances. The moderate rise in the temperature, the absence of vomiting and the subsequent history of the case confirmed the diagnosis of antitoxine rash. An eruption resembling measles has been noticed a few times. From the appearance of this eruption it would be impossible to make a differential diagnosis, but the absence of constitutional symptoms has been an aid in deciding upon the nature of the eruption.

In the mixed cases of scarlet fever and diphtheria, antitoxine has had a beneficial effect upon the diphtheritic membrane, but of course has had no effect on the attack of scarlet fever. In addition to the use of antitoxine, alcoholic stimulation has been very freely used; digitalis, strychnia and atropia have been used in suitable cases. Milk has been the principal article of diet, and has been given in as

large quantities as the patient could be induced to take. In certain cases where the patients absolutely refused to take food and stimulants, nasal feeding has been tried, and in some instances this seemed to be the turning point, and the patient's life was apparently saved by this procedure. It is not sufficient to simply give antitoxine and do nothing else for the relief of the patient. In no disease are food and stimulants more imperatively demanded than in diphtheria, and an attempt has been made to give food and stimulants in any way in which they could be absorbed. A word may be said regarding nasal feeding. It is less annoyance to the patient, it causes less strain on the nervous system in some instances to give food by the nasal tube than by the mouth. The constant endeavor to make a patient take food by the mouth is a much greater injury to him than the passage of a small rubber catheter through the nose into the stomach. The beneficial effects of this method of feeding have been illustrated in so many instances at the hospital, that I may be pardoned for alluding to it in somewhat strong terms. The less you annoy a patient ill with diphtheria the better for him. There is no doubt in my mind that many a diphtheria patient has been hurried to death by over zealous attempts to induce him to take nourishment.

Irrigation with a hot saline solution, and in some cases a solution of corrosive sublimate one part to ten thousand, has been the application that has been used for the nose and throat, and the relief experienced by patients from this has been very marked. The less one interferes with the membrane the better for the patient. The irrigation removes all particles of membrane that are easily detached, and does not leave an abraded surface to serve as a focus for the extension of the membrane. The forcible detachment of the membrane by forceps cannot be too strongly deprecated. The use of caustics is of no advantage.



The experiments of Roux and Yersin show conclusively that diphtheritic membrane is less likely to extend on intact mucous membrane than on abraded surfaces, and therefore when the mucous membrane is in anyway injured an opportunity is given for the extension of the disease.

Albuminuria has not been increased to any considerable extent by the use of antitoxine. An analysis of eighty-three cases at the hospital, in which the urine was examined before and after antitoxine was administered, showed that in thirty-eight cases albumen was absent; that in thirty cases there was the same amount of albumen before and after antitoxine was given; that in eleven cases albumen was diminished after the injection, and that in four cases albumen was increased. Of these four cases, in two the amount of the increase was from nothing to the slightest possible trace, and in two the amount was increased from a trace to a large trace. In no instance have renal complications given rise to serious symptoms. Albuminuria is such a frequent complication in diphtheria that any statistics, to be of value regarding the action of antitoxine on this condition, must embrace a great number of cases, and the examination of the urine must be made before and after the administration of the agent. Observers who have claimed that antitoxine causes albuminuria in diphtheria have in many instances failed to test the urine before antitoxine was used, and many of these observers lose sight of the fact that albuminuria is one of the most constant symptoms in severe cases of diphtheria.

No cases of anuria have been observed at the hospital.

Paralyses have been observed in a comparatively small number of cases, the percentage being somewhat less than was noted before the days of antitoxine. When the cases have been received early in the history of the attack, before the growth of the organism was sufficient to generate a great amount of toxine, paralysis has not as a rule occurred.

If, on the other hand, the case was received late in the course of the disease and the membrane was extensive, paralysis more or less marked has occurred in the majority of cases. Cases of sudden death so common in the convalescence of diphtheria have not occurred, but there have been a few cases in which after apparent convalescence there would be an attack of vomiting and the patient rapidly lose strength and gradually sink and die in from 24 to 72 hours from the commencement of the attack. Broncho-pneumonia has been one of the most frequent causes of death, and no one claims that antitoxine has any remedial power in this condition. If all the cases of death from broncho-pneumonia were eliminated, the death-rate from diphtheria pure and simple, when antitoxine is used, would be much lower than that that has been previously given.

In the laryngeal cases intubation has been the operation generally selected, as this operation has in every instance relieved the stenosis. The advantages of intubation are first, a minimum amount of shock, and second, there are no cut surfaces to afford soil for the growth of not only the diphtheria bacilli but of other bacteria, for no matter how carefully you may carry out aseptic precautions it is impossible to keep a tracheotomy wound aseptic as can be done in other surgical operations. There can be no doubt that the fatal issue in cases of tracheotomy is due in most instances to an infection either through the wound or through the orifice of the tube itself. In the few cases of tracheotomy at the hospital, death was caused by this very infection. Another advantage of the intubation tube is the fact that the air that enters the lungs passes through the natural channels and therefore is less likely to irritate these organs. One argument that has been used against intubation is that the patient is unable to take the requisite amount of food; but this is obviated by the use of nasal

feeding, which has been a very important factor in reducing the death-rate. That antitoxine has also been a very important factor no one can reasonably doubt who has observed intubation cases before antitoxine was used and since its adoption.

The site of the injection has been in some instances the outer aspect of the middle third of the thigh, the lumbar region and the upper third of the thorax near the posterior axillary line. After a careful consideration of these various positions, it seems to me that the last situation is the best, for the reason that any irritation and swelling in this locality causes less annoyance to the patient than in either of the other localities. One very important advantage is also that in this place the nervous distribution is comparatively limited, and therefore the amount of pain is diminished to a minimum. The technique of the operation is as follows: First, the parts are rendered aseptic by washing with corrosive sublimate; second, the syringe and needle are carefully sterilized by boiling. The antitoxine is strained into the barrel of the syringe through sterile gauze. A fold of the skin is taken up by the thumb and fore finger, and the needle plunged deeply into the cellular tissue. The injection is then made slowly and carefully with only a limited amount of force. After the needle is removed the opening in the skin is sealed with gauze and collodion. If the injection is properly given there should be no tumor and therefore no necessity of rubbing the parts in order to cause the disappearance of the tumor as is recommended by certain observers. Williams's syringe, which consists of a glass barrel and a glass piston with asbestos packing, is the instrument that has been used. Koch's syringe, which consists of a glass barrel with a detachable rubber bulb, is a very good instrument for this purpose. L  ter manufactures a very good syringe. One advantage of L  ter's syringe is, that there is no packing to become worn, as the piston is



carefully ground to fit the barrel. The only objection to this syringe is its high cost. As a matter of fact it makes very little difference what kind of a syringe is used so long as each and every part can be thoroughly and absolutely sterilized by heat without injury. A small needle should always be used, for with a minute puncture the danger of infection is diminished.

The preparation of antitoxine, and its use in the treatment of diphtheria, are the results of careful and laborious work of bacteriologists, and whatever advantage has been gained in the treatment of diphtheria is due to the science of bacteriology. It has been claimed that the use of antitoxine is unscientific, but any one who has carefully read the reports of Roux, Yersin, Aronson and many others cannot fail to be struck with the eminently scientific nature of their work. As the preparation of antitoxine requires great scientific knowledge and an unlimited amount of time and patience, it is evident that in order to be a success, from a commercial point of view, the price must be so high as to place it out of the reach of the poorer classes, and therefore it is incumbent on State and City Boards of Health to make arrangements whereby the serum can be distributed gratuitously or sold at a nominal price. As has been before stated, all the antitoxine used at the hospital has been prepared by Dr. Ernst, and there can be no doubt that the satisfactory results obtained have been due to the excellence of this preparation and the careful manner in which it has been prepared.

In this paper a short and imperfect account of the work in the diphtheria wards of the hospital has been outlined, and certainly a diminution of the death-rate from 46 per cent. when antitoxine was not used, to one of 12.50 when it was used, can only be explained by the remedial power of this agent. If many cases of death occurring in persons ill of diphtheria, but in whom the cause of death was other

than diphtheria, had been eliminated, the death-rate would have been much lower; but as it has been the object of this paper to show the true value of antitoxine, in the treatment of diphtheria, it has been deemed advisable to err against antitoxine rather than for it.